Claims 72, 96, and 125 stand rejected under 35 USC §112 as being indefinite, the Examiner having taken the position that the claims omit essential elements, and stated that "...the specification has required that sustained release or delayed release embodiments be included in the dosage forms, such as matrix systems, however the above claims do not contain such an element.

The rejection is traversed and/or not understood. Applicants claims, on their face, require sustained release, as claimed in claims 72 and 125, or delayed release, as claimed in claim 96. The claims are limited to azithromycin as the antibiotic. The dependent claims define various embodiments of each, such as the matrix sustained release dosage form alluded to by the Examiner (e.g., see claim 73). However, there is no reason, in Applicants view, to incorporate "matrix" (or any other specific embodiment defined in the dependent claims) into the independent claims. Such an amendment is not required to distinguish over the prior art, and it is otherwise for the inventor to decide what bounds of protection he will seek. In re Wertheim, 191 USPQ 90, 97 (CCPA 1976). The dependent claims otherwise define the sustained release and/or delayed release embodiments referred to by the Examiner. MPEP 2172.01 is not applicable here because Applicants have not omitted matter essential to the invention from the claims. Indeed, "matrix", as it applies to sustained release embodiments, is only one of many embodiments disclosed by Applicants for practicing the invention.

Claims 72 and 125 stand rejected under 35 USC §112 as indefinite. The Examiner contended that the claims do not state that the dosage form contains a certain amount of azithromycin, or even if azithromycin is included in the dosage form.

In response, Applicants have amended claims 72 and 125 to state "...a dosage form comprising azithromycin...", in contrast to the former language "...a dosage form of azithromycin..." The amendatory language makes it clear that the dosage form includes azithromycin. Although claim 96 was not similarly rejected, that claim has been amended in parallel for consistency.

So far as including the amount of azithromycin is concerned, it is Applicants position that including the amount is not necessary. The invention as defined in claims 72 and 125 does not depend on the exact amount of azithromycin in the dosage form. Rather, it depends, *inter alia*, on the release rate which is embodied in the claims. Applicants' specification is quite clear and informative that it is the release rate that is important, not the absolute amount of azithromycin. See page 4, lines 9-15 where it is stated

> It is noted that, although the temporal and weight criteria define a release profile extending for as long 6 hours, a dosage form according to the invention can release substantially all of its azithromycin well before 6 hours, so long as it otherwise fits within the defined rates. Dosage forms according to the invention which contain relatively low amounts of azithromycin (e.g., less than 1000 mg) may well release substantially all their azithromycin within a few hours.

Thus it is respectfully submitted that the claims are clear and definite as amended.

Claims 72-76, 80-86, 93-130, 133-149, and 146-148 continue to be rejected under 35 USC §112 as obvious over Curatolo (US 5, 605,889), further in view of Handsfield (ICAAC Program and Abstracts), Urquhart (US 4,851,231), and Edgren (US 4,522,625). The Examiner cited the USP dissolution test from Curatolo, the treatment of gonorrhea with azithromycin disclosed in Handsfield, the fact that certain drugs such as erythromycin can induce nausea (Urquhart), and the prolonged release device taught by Edgren. The Examiner included arguments intended to refute Applicants' previous response in which Applicants argued that there was no motivation to combine the references, and that the rejection was based on hindsight.

Applicants continue to traverse the rejection based on the grounds set forth in the previous rejection, but will try to explain these grounds in different words. The Examiner, in the present Office Action, quoted much of the material which supports the instant traversal.

First, it is repeated that Applicants' invention is related to controlled release dosage forms, i.e., dosage forms which meter azithromycin out slowly or which contain a mechanism to delay its release. By contrast, Curatolo 5,605,889 is related to immediate release dosage forms, i.e., those dosage forms which release azithromycin without any mechanism for intentionally prolonging or delaying its release. The Examiner himself confirmed this fact by quoting the USP *in vitro* dissolution test disclosed in Curatolo. That test (see page 3 of the Office Action) requires that the dosage forms therein exhibit 90% dissolution within about 30 minutes when an amount of dosage form equivalent to 200 mg is tested. The instant application makes it abundantly clear that such immediate release dosage forms are not within the scope of Applicants' claims. See page 2, lines 21 – 24 where it is stated:

> The term "controlled" is generic to "sustained" and "delayed". Dosage forms which release more than 70% of their contained azithromycin within one half hour or less are not "controlled release", and form no part of this invention.

Thus Applicants continue to rely on their previous grounds of traversal - - that it makes no sense to combine a reference related solely to immediate release (Curatolo) with references that deal with controlled release (Urquhart and Edgren). One of ordinary skill in the art interested in controlled release dosage forms would undoubtedly dismiss Curatolo out of hand as irrelevant and/or be led away from the invention. Similarly, Applicants continue to maintain that the only reason for making a rejection involving Curatolo must be based on hindsight. The only thing Curatolo has in common with the instant application is that it uses azithromycin. The dosage forms disclosed and claimed in Curatolo are opposite to the ones instantly claimed.

Further, the secondary references do not otherwise fill in the gaps left by Curatolo. None of them makes any suggestion to put azithromycin in a controlled release dosage form. In this respect, Edgren and Urquhart are simply examples of controlled release dosage forms, but with no suggestion to put azithromycin in a controlled release dosage form. Handsfield simply demonstrates that azithromycin is a good, effective antibiotic.

The Examiner is respectfully urged to reconsider and withdraw his grounds of rejection, and to allow the instant application. The art on which the rejection is based either leads away (immediate release, Curatolo) and fails otherwise to make any suggestions that would render the instant invention obvious.

In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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VERSION MARKED UP TO SHOW CHANGES MADE

72. A sustained release dosage form comprising [of] azithromycin which meets the following in vitro criteria:

(1) $Q_{0.25} \leq$ 200 mg,

(2) $Q_1 \leq$ 500 mg,

(3) $Q_2 \leq$ 1000 mg,

(4) $Q_4 \leq$ 1500 mg, and

(5) $Q_6 \leq$ 2000 mg,

when said dosage form is tested in a USP rotating paddle apparatus, said apparatus being described in USP XXIII dissolution test chapter 711, and wherein the apparatus has paddles rotating at 50 rpm and contains 900 mL of pH 6.0 sodium dihydrogen phosphate buffer at 37°C;

and wherein, if said dosage form is a capsule, said buffer is implemented to contain 0.1 mg/mL of trypsin.

96. A delayed release dosage form comprising [of] azithromycin which meets the following in vitro criteria:

in a first dissolution stage, $Q_{0.25} < 10\%$ when said dosage form is inserted in a USP rotating paddle apparatus, said apparatus being described in USP XXIII dissolution test chapter 711, and wherein said apparatus has paddles rotating at 50 rpm and contains 750 mL of 0.1 N HCl at 37°C;

in a second dissolution stage, $Q_{0.5} < Q_{0.25} + 10\%$ when 250 mL of 0.2 M tribasic sodium phosphate buffer is added to said acid immediately following said first stage to implement a buffer having a pH of about 6.8.

125. A sustained release dosage form comprising [of] azithromycin for ingestion by a mammal which meets, based on the weight of said mammal, the following in vitro criteria:

(1) $Q_{0.25} \leq$ 4 mg/Kg of mammal weight,

(2) $Q_1 \leq$ 10 mg/Kg of mammal weight,

(3) $Q_2 \leq$ 20 mg/Kg of mammal weight,

(4) $Q_4 \leq$ 30 mg/Kg of mammal weight, and

(5) $Q_6 \leq 40$ mg/Kg of mammal weight,

when said dosage form is tested in a USP rotating paddle apparatus, said apparatus being described in USP XXIII dissolution test chapter 711, and wherein the apparatus has paddles rotating at 50 rpm and contains 900 mL of pH 6.0 sodium dihydrogen phosphate buffer at 37°C;

and wherein, if said dosage form is a capsule, said buffer is implemented to contain 0.1 mg/mL of trypsin.